Letter to the Editor

American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Omalizumab-Associated Anaphylaxis Joint Task Force follow-up report

To the Editor:

In 2007, a Joint Task Force of the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology was formed (Omalizumab Joint Task Force [OJTF]) with the purpose of reviewing the omalizumab (Xolair; Genentech/Novartis, Basel, Switzerland) clinical trials and postmarketing surveillance data on anaphylaxis, either reported as such or reported by using terms such as anaphylactoid reaction, multisystem allergic reaction, systemic allergic reaction, and infusion reaction. The OJTF review focused on postmarketing data from June 2003 to December 2006 by using the definition of anaphylaxis and the clinical criteria for diagnosis of anaphylaxis developed in a multidisciplinary symposium and published in 2006.[1] The OJTF found that anaphylaxis occurred in approximately 0.09% of patients receiving omalizumab injections and further ascertained that 61% of these reactions occurred within the first 2 hours after the first 3 injections and 14% occurred within 0.5 hours after the fourth or later injection. The OJTF report published in 2007 recommended 5 steps for physicians prescribing omalizumab (Xolair) injections to consider to ensure the safety of patients receiving omalizumab injections (Table I).[2]

After publication of this report, the OJTF continued to review the postmarketing safety data provided by Genentech/Novartis with the intent of updating these recommendations if significant changes were identified in the pattern of adverse events after omalizumab (Xolair) injections.

The OJTF also met regularly with scientific representatives of Genentech/Novartis on several occasions to review the Risk Evaluation Mitigation Strategy (REMS) for omalizumab (Xolair) approved by the US Food and Drug Administration (FDA).[3] The following report summarizes the OJTF's ongoing safety surveillance findings and the omalizumab (Xolair) REMS. It does not include any revisions to the recommendations in the original task force report because no clinically significant additional observations related to omalizumab-associated anaphylaxis were made.

Genentech/Novartis provided the OJTF with 127 postmarketing case reports of possible omalizumab (Xolair)–associated anaphylaxis filed with the FDA that occurred from January 1, 2006, to December 31, 2008. Cases might be underreported[4] or not labeled as anaphylaxis.[5] Four members of the OJTF reviewed the reports using the same consensus definition of anaphylaxis used to assess cases in the initial report.[1] The reviewers classified the cases in terms of being omalizumab-associated anaphylaxis as either likely, probably, very unlikely, or not enough information. Cases judged by at least 2 reviewers to be likely or probably omalizumab-associated anaphylaxis were further analyzed. This additional analysis included several questions (Table II) aimed at determining whether there were any markers or trends among these reactions (eg, prior history of drug or food allergy, gap between omalizumab injections, and serum tryptase measurements), as well as how the reactions were treated (eg, epinephrine, emergency department visits, and hospitalizations).

Reviewers classified 77 of the 127 cases as likely or probably omalizumab-associated anaphylaxis. The timing of the reactions in relationship to the dose pattern was virtually unchanged from the previous report (Table III).[2] Assuming that the postinjection observation times recommended in the previous report were observed, approximately 77% of the reactions likely occurred in a medical facility. Scrutiny of these cases did not reveal any particular markers or trends that identified patients at risk. Serum tryptase levels, reflecting mast cell activation, were measured in only 8 of the 127 cases, with no increases reported in 6 cases and no test results available in the remaining 2 cases. This underscores some of the difficulties in reviewing these postmarketing case reports. It is important to note that all of the data are based on the information in the adverse event report forms supplied to Genentech/Novartis. The amount and quality of information supplied by the physicians, nurses, pharmacists, or other health care professionals who filled in the forms varied greatly.

When an adverse event form is received, an attempt is made to contact the physician, and if permission is granted, an attempt is made to contact the patient described in the form. However, some of these attempts are unsuccessful, and even when further information is gathered, it is often sparse.

Collectively, these factors make adverse event forms difficult to interpret. Although a widely accepted consensus definition for anaphylaxis was used to interpret the adverse event reports, there were many difficulties in being certain that an adverse event was anaphylaxis. For example, all the patients treated with omalizumab (Xolair) had asthma. In many of the events, a patient was reported to have wheezed several hours after the injection and also to have experienced a sensation of warmth or mild flushing (without pruritus). It is impossible to ascertain whether such patients had an acute asthma episode or an anaphylactic episode.

Among the OJTF reviewers, there was wide variation in interpretation of some events, with a trend toward being conservative and erring on the side of attributing clinical significance to events that were not clearly reported but that might have been anaphylaxis. Thus it is highly likely that there was overreporting

TABLE I. Summary of the joint task force's 2007 recommendations*

1. **Informed consent**: should be obtained from the patient after discussing the risks, benefits, and alternatives to omalizumab (Xolair).
2. **Anaphylaxis education**: educate the patient on the signs, symptoms, and treatment of anaphylaxis.
3. **Epinephrine autoinjector**: prescribe and educate the patient on the proper use of and advise patients to carry an epinephrine autoinjector before and for 24 hours after omalizumab (Xolair) injection.
4. **Preinjection health assessment**: assess health status, including vital signs and some measure of lung function (eg, peak expiratory flow or FEV_1).
5. **Wait period after injection**: patients should be kept under observation for 30 minutes after each injection. This time should be extended to 2 hours after each of the first 3 injections; however, it could be modified based on a physician's clinical judgment after discussing the risks with the patient.

*Adapted from Cox et al.[2]

TABLE II. Questions considered in reviewing the cases of likely or probably omalizumab treatment–associated anaphylaxis (n = 77)

Reaction characteristics
Omalizumab (Xolair) dose?
Timing?
First signs and symptoms?
Protracted reaction?
Biphasic reaction?
Was tryptase drawn?
Risk factors
History of anaphylaxis vs no prior history?
History of drug allergy?
History of latex allergy?
History of food allergy?
Medications
β-Blockers?
Angiotensin-converting enzyme inhibitors?
Acetylsalicylic acid? Other nonsteroidal anti-inflammatory drug?
Other?
Potential predisposing factors
Lack of adequate omalizumab (Xolair) mixing?
Recent (within 1 week) respiratory tract infection?
Increased asthma symptoms or exacerbation?
Was the patient premedicated?
Was the patient rechallenged after the reaction?
Was there a gap in omalizumab (Xolair) injections?
What treatment was administered for the acute reaction?
Epinephrine?
Oxygen?
Antihistamine?
Inhaled β-agonist?
Emergency department visit?
Hospitalization?
Intensive care unit admission?
Other?

TABLE III. Summary of reaction timing in comparison with omalizumab (Xolair) dose and recommended wait period

Dose	Patients*	Total with known timing	Reactions occurring within the recommended wait period†‡	Reactions occurring beyond the recommended wait period‡	Timing unknown
1-3	44	40	33 (82%)	7 (18%)	4
4 and subsequent	33	29	20 (68%)	9 (32%)	4
Total	77	69	53 (77%)	17 (23%)	8

*Number reflects patient numbers and not numbers of reactions. Some patients had more than 1 reaction, and only the first reaction was included unless the subsequent reaction was the primary reason for the reporting.
†Recommended wait period after omalizumab (Xolair) injection per the OJTF 2007 report: 2 hours after the first 3 doses and 30 minutes after subsequent injections.[2]
‡Percentage of patients with known timing.

of anaphylactic episodes because of the conservative nature of the review. In reality, some of these events might have been due to other problems, including the patients' underlying poorly controlled asthma, which was the indication for omalizumab (Xolair) treatment. The exact incidence of such overreporting cannot be established because of the lack of information provided.

The FDA was given the authority by the FDA Amendments Act of 2007 to require REMSs from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks. In keeping with the REMS program for omalizumab, the FDA requested that an attempt be made to develop a skin test, an *in vitro* test, or both that would detect patients at risk of a reaction and distinguish them from those who could be given the agent without experiencing an adverse event. A protocol was therefore designed to determine whether a skin test to omalizumab could be validated as a means of detecting patients who were at risk of a reaction after injection. The goal of the initial phase of this protocol was to see whether a concentration of omalizumab could be found that would not produce an irritant reaction, an adverse event, or a detectable IgG response to omalizumab. Skin testing was performed in healthy control subjects and allergic asthmatic patients who had not previously been exposed to omalizumab to assess this. It was found that skin testing could be performed without irritant responses, adverse events, or the development of detectable IgG antibodies to omalizumab. Moreover, it was found that skin prick testing to omalizumab could be accomplished by using various dilutions without producing an irritant response, and an intradermal test with an omalizumab concentration of 1:100,000 (containing 1.2 μg of omalizumab per milliliter) could also be safely performed without producing an irritant response.[6] In the future, this skin test protocol will be useful for evaluating patients who have experienced possible omalizumab-associated anaphylaxis.

In summary, based on the OJTF's ongoing postmarketing safety surveillance for omalizumab injections, there does not appear to be any change in the pattern of omalizumab-associated anaphylactic episodes, which continue to be reported infrequently. Assuming that the task force's previous recommendations for observation times were followed, approximately 77% of these reactions likely occurred in a supervised medical facility. Thus no change from the previous task force report's wait period recommendations is being proposed. In addition to the suggested observation times, the original report stressed the importance of several patient safety–related interventions that the OJTF continues to believe are important to implement. These include the following: obtaining informed consent, performing a preinjection health assessment, requiring a 2-hour observation period after the first 3 injections and a 30-minute observation period after subsequent injections, providing regular patient education about anaphylaxis, and prescribing 1 or more epinephrine autoinjectors with training on proper use.

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Disclosure of potential conflict of interest: L. Cox has consultant arrangements with Stallergenes, Genentech/Novartis, and ISTA Pharmaceuticals; receives research support from Stallergenes; is Secretary/Treasurer of the American Academy of Allergy, Asthma & Immunology; is on the Board of Directors for the American Board of Allergy and Immunology; and is a member of the Joint Task Force on Practice

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